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## **Efficacy, safety, and tolerance of piperacillin/tazobactam compared to co-amoxiclav plus an aminoglycoside in the treatment of severe pneumonia**

Speich, R ; Imhof, E ; Vogt, M ; Grossenbacher, M ; Zimmerli, W

**Abstract:** An open, randomized, multicenter study was conducted to compare the efficacy and safety of piperacillin/tazobactam and co-amoxiclav plus aminoglycoside in the treatment of hospitalized patients with severe community-acquired or nosocomial pneumonia. Of the 89 patients who entered the study, 84 (94%) were clinically evaluable. A favorable clinical response was observed in 90% of the piperacillin/tazobactam group and in 84% of the co-amoxiclav/aminoglycoside group (not significant). The bacteriological efficacy was comparable in both groups (96% vs. 92%; not significant). There was only one fatal outcome in the piperacillin/tazobactam group compared to six in the co-amoxiclav/aminoglycoside group (regimen  $P=0.058$ ). The adverse event rate was non-significantly lower in the piperacillin/tazobactam group compared to the co-amoxiclav/aminoglycoside group (2% vs. 7%;  $P=0.32$ ). Piperacillin/tazobactam is safe and highly efficacious in the treatment of serious pneumonia in hospitalized patients. It compares favorably with the combination of co-amoxiclav/aminoglycoside

DOI: <https://doi.org/10.1007/bf01709453>

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ZORA URL: <https://doi.org/10.5167/uzh-156573>

Journal Article

Published Version

Originally published at:

Speich, R; Imhof, E; Vogt, M; Grossenbacher, M; Zimmerli, W (1998). Efficacy, safety, and tolerance of piperacillin/tazobactam compared to co-amoxiclav plus an aminoglycoside in the treatment of severe pneumonia. *European Journal of Clinical Microbiology Infectious Diseases*, 17(5):313-317.

DOI: <https://doi.org/10.1007/bf01709453>

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*Article*

# Efficacy, Safety, and Tolerance of Piperacillin/Tazobactam Compared to Co-Amoxiclav plus an Aminoglycoside in the Treatment of Severe Pneumonia

R. Speich, E. Imhof, M. Vogt, M. Grossenbacher, W. Zimmerli

**Abstract** An open, randomized, multicenter study was conducted to compare the efficacy and safety of piperacillin/tazobactam and co-amoxiclav plus aminoglycoside in the treatment of hospitalized patients with severe community-acquired or nosocomial pneumonia. Of the 89 patients who entered the study, 84 (94%) were clinically evaluable. A favorable clinical response was observed in 90% of the piperacillin/tazobactam group and in 84% of the co-amoxiclav/aminoglycoside group (not significant). The bacteriological efficacy was comparable in both groups (96% vs. 92%; not significant). There was only one fatal outcome in the piperacillin/tazobactam group compared to six in the co-amoxiclav/aminoglycoside group regimen ( $P=0.058$ ). The adverse event rate was non-significantly lower in the piperacillin/tazobactam group compared to the co-amoxiclav/aminoglycoside group (2% vs. 7%;  $P=0.32$ ). Piperacillin/tazobactam is safe and highly efficacious in the treatment of serious pneumonia in hospitalized patients. It compares favorably with the combination of co-amoxiclav/aminoglycoside.

## Introduction

Piperacillin is a semi-synthetic penicillin with a broad spectrum of antibacterial activity. Administered parenterally, it has been widely used in the treatment of serious infections, including pneumonia [1–3]. However, the growing prevalence of  $\beta$ -lactamase-producing or-

ganisms increasingly limits the clinical efficacy of piperacillin as monotherapy [4]. Tazobactam, a recently developed penicillanic acid sulfone, irreversibly inhibits a wide range of bacterial  $\beta$ -lactamases. Consequently, tazobactam prevents the inactivation of piperacillin by  $\beta$ -lactamase-producing microorganisms such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella pneumoniae*, and anaerobes [5–7].

In two recent trials, the combination of piperacillin and tazobactam was effective, well tolerated, and safe in the treatment of hospitalized patients with pneumonia [8, 9]. Furthermore, two randomized, comparative, multicenter trials indicate that piperacillin/tazobactam is as effective as cefuroxime and more effective than ceftazidime in this same indication (A.P. Pallett and M.P. Carroll, 6th International Congress for Infectious Diseases, Prague, 1994, Abstract no. 857; M. Joshi et al., 6th International Congress for Infectious Diseases, Prague, 1994, Abstract no. 856). The present study was designed to compare the efficacy, tolerance, and safety of piperacillin/tazobactam with that of co-amoxiclav plus aminoglycoside in patients with serious community-acquired or nosocomial pneumonia.

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## Materials and methods

**Entry Criteria.** Participants included patients of either sex  $\geq 16$  years of age with pneumonia defined by the presence of three criteria: i) body temperature  $>38^{\circ}\text{C}$ ; ii) new or progressive infiltrates on chest radiographs or focal signs on physical examination of the chest, and iii) at least two of the following: new onset of purulent sputum ( $\geq 25$  leukocytes and  $\leq 10$  epithelial cells per low power microscopical field) or signs of infection (elevated C-reactive protein, elevated erythrocyte sedimentation rate, leukocytosis); respiratory pathogen isolated from blood culture; isolation of pathogen from sputum or specimen obtained by bronchoalveolar lavage, bronchial brushing or biopsy. The severity of the changes on the initial chest radiographs was scored as follows: 1, mild: unilobar infiltrates; 2, moderate: bilobar infiltrates; 3, severe: bilateral infiltrates. Only patients with at least one of the following criteria indicating nosocomial or serious infections were included: i) hospital-acquired infection (at least 48 h after admission); ii) underlying disease (diabetes, alcoholism, chronic bronchitis, collagen vascular disease); iii) the presence of at least two of the following clinical signs: diastolic blood pressure  $\leq 60$  mmHg; respiratory rate  $\geq 30$ /min;  $\text{PaO}_2 \leq 6.6$  kPa.

Exclusion criteria included known allergy to any of the study drugs; history of cystic fibrosis, tuberculosis, or respiratory tract carcinoma; antibiotic therapy within 12 h of enrollment; HIV infection; neutropenia ( $<1000/\text{mm}^3$ ) or thrombopenia ( $<50000/\text{mm}^3$ ); septic shock; hemodialysis, peritoneal dialysis, plasmapheresis or hemoperfusion; elevated serum transaminases, alkaline phosphatase or bilirubin ( $>3$  above the normal values); previous treatment with piperacillin/tazobactam or co-amoxiclav/aminoglycoside during the present hospital stay; pregnancy or breast feeding.

**Study Design.** This open, randomized, comparative study was conducted in five hospital centers in Switzerland. Patients were randomized to receive either piperacillin/tazobactam or co-amoxiclav/aminoglycoside in a 1:1 ratio according to a computer-derived program. Both regimens were administered as 30-min i.v. infusions. The piperacillin/tazobactam treatment consisted of a combination of 4 g of piperacillin and 500 mg of tazobactam at 8 h intervals, while the co-amoxiclav/aminoglycoside group received a combination of 2 g of amoxicillin and 200 mg of clavulanic acid at 8 h intervals, plus a single dose of 3–6 mg/kg of aminoglycoside (netilmicin or gentamicin). The patients were to be treated for a minimum of 48 h and a maximum of 21 days.

**Outcome Measures.** During the period of antibiotic treatment, routine clinical evaluations were performed daily during the first week, and every 2 to 3 days thereafter. Laboratory parameters were determined on day 4 and on the last day of treatment. Bacteriological cultures were repeated on day 4 and, if possible, at the cessation of the study, and all concomitant therapy was recorded in detail. Ten to 14 days following the cessation of treatment, the patient's general status was assessed.

The clinical response to therapy was classified as follows: non-assessable,  $<48$  h of therapy; cure, clinical response with disappearance of fever, tachypnea, and other clinical signs (except for chest x-ray) and symptoms during the treatment period; improvement, marked reduction of the signs and symptoms of infection, without complete resolution; relapse, adequate initial response followed by a worsening of the clinical condition due to the occurrence of a bacterial or fungal infection within 7 days of stopping treatment; failure, no response to at least 48 h of antibiotic therapy, worsening of the clinical condition due to infection, or death.

The bacteriological efficacy was assessed in patients treated for at least 48 h and exhibiting one or more baseline pathogens according to the following classification: documented eradication, all baseline pathogens eradicated and no new pathogens present in fol-

low-up cultures; presumed eradication, no repeat sputum sample could be obtained in a patient with a favorable clinical response; documented persistence, any baseline pathogen was present in a culture or cultures obtained from any site of infection upon completion of therapy; presumed persistence, unfavorable clinical outcome, but no follow-up cultures were available; super-infection, all baseline pathogens were eradicated, but one or more new pathogens appeared in the follow-up cultures; indeterminate, switch of antibiotic therapy, concomitant antibiotic therapy for reasons other than failure, death during therapy for a reason not related to the infection, or  $<48$  h of therapy.

All adverse events occurring during the trial were recorded. The possible relationship of an adverse event to treatment was assessed as definite, probable, possible, remote, not related, or unknown. The safety analysis was performed on all patients who were enrolled in the study (intent-to-treat).

**Statistical Methods.** All values are presented as the mean  $\pm$  SD. Frequencies and categories were compared using Fisher's exact test. The Mann-Whitney U test was used for continuous variables. A  $P$  value  $<0.05$  was considered significant.

## Results

**Patient Characteristics.** A total of 89 patients were enrolled: 44 in the piperacillin/tazobactam group and 45 in the co-amoxiclav/aminoglycoside group. The two groups were highly comparable regarding demographic characteristics, clinical signs, and laboratory as well as radiographic parameters of severity of pneumonia (Table 1). Ten patients had nosocomial pneumonia and 79 serious community-acquired pneumonia.

**Clinical Efficacy.** For the clinical efficacy evaluation, five patients had to be excluded (3 in the piperacillin/tazobactam group and 2 in the co-amoxiclav/aminoglycoside group) for the following reasons: treatment duration less than 48 h ( $n=4$ ), and erroneous inclusion of a patient with urinary tract infection ( $n=1$ ). The mean duration of antibiotic therapy in all patients was 10.2 days for the piperacillin/tazobactam group and 10.1 days for the co-amoxiclav/aminoglycoside group. In the clinically evaluable patients, the mean duration of treatment was 10.7 days for the piperacillin/tazobactam group and 10.5 days for the co-amoxiclav/aminoglycoside group.

The results of the clinical efficacy evaluation (84 patients) are presented in Table 2. Clinical cure was achieved in 33 (81%) of the patients treated with piperacillin/tazobactam and in 28 (65%) of the patients who received co-amoxiclav/aminoglycoside ( $P=0.091$ ). An overall favorable clinical response (cure or improvement) was observed in 37 (90%) of the piperacillin/tazobactam patients and in 36 (84%) of the co-amoxiclav/aminoglycoside patients ( $P=0.288$ ). There were three (7%) treatment failures in the piperacillin/tazobactam group and six (14%) in the co-amoxiclav/aminoglycoside group ( $P=0.266$ ). One patient in each group relapsed.

**Table 1** Demographic characteristics and clinical data at presentation of patients treated with either piperacillin/tazobactam or co-amoxiclav/aminoglycoside

Characteristic	PIP/TAZ group (n = 44)	Co-AMX/amino group (n = 45)	P value
Age (years)*	64.7 ± 18.7	64.6 ± 17.0	>0.5
Nosocomial pneumonia	4/4	6/45	0.38
Temperature (°C)*	38.9 ± 0.8	38.6 ± 0.9	0.11
Leukocytes (10 <sup>9</sup> /l)*	13.7 ± 6.1	15.0 ± 6.6	0.48
C-reactive protein (mg/l)*	185 ± 104	186 ± 125	>0.5
Serum urea (mmol/l)*	12.2 ± 25	17.1 ± 39.1	0.47
Albumin (g/l)	35 ± 7	34 ± 8	>0.5
Radiographic score*	2.3 ± 0.8	2.3 ± 0.7	>0.5

\* Values expressed as mean ± SD.

PIP, piperacillin; TAZ, tazobactam; Co-AMX, co-amoxiclav; amino, aminoglycoside

**Table 2** Clinical efficacy in evaluable patients treated with either piperacillin/tazobactam or co-amoxiclav/aminoglycoside

Outcome	No. (%) of patients		P value
	PIP/TAZ group (n = 41)	Co-AMX/amino group (n = 43)	
Cure <sup>a</sup>	33 (81)	28 (65)	0.09
Improvement <sup>b</sup>	4 (10)	8 (19)	0.2
Relapse <sup>c</sup>	1 (2)	1 (2)	>0.5
Failure <sup>d</sup>	3 (7)	6 (12)	0.26

<sup>a</sup> Clinical response with disappearance of fever, tachypnea, and other clinical signs (except for chest x-ray) and symptoms during the treatment period.<sup>b</sup> Marked reduction of the signs and symptoms of infection, without complete resolution.<sup>c</sup> Adequate initial response followed by a worsening of the clinical condition due to the occurrence of a bacterial or fungal infection within 7 days of stopping treatment.<sup>d</sup> No response to at least 48 h of antibiotic therapy, worsening of the clinical condition due to infection, or death.

PIP, piperacillin; TAZ, tazobactam; Co-AMX, co-amoxiclav; amino, aminoglycoside.

Whereas there was one death in the piperacillin/tazobactam group, six deaths occurred among patients receiving co-amoxiclav/aminoglycoside ( $P=0.0586$ ;  $P=0.0584$  in the intent-to-treat analysis, which included all 89 patients). All causes of death were attributable to pneumonia, either due to respiratory failure, irreversible septic shock, or multiple organ failure. None of these deaths were attributed to the study medication.

**Bacteriological Efficacy.** For the analysis of bacteriological efficacy, it was necessary to exclude 19 patients in the piperacillin/tazobactam group and 18 patients in the co-amoxiclav/aminoglycoside group. Bacteriological non-evaluability was due to the absence of a baseline pathogen ( $n=32$ ), treatment duration of less than 48 h ( $n=4$ ), and incorrect diagnosis ( $n=1$ ). Bacteria were isolated in 25 of the 41 clinically evaluable patients (61%) in the piperacillin/tazobactam group and in 27 of the 43 evaluable patients (63%) in the co-amoxiclav/aminoglycoside group. The majority of the patients were infected with a single pathogen; four patients had two pathogens, and one patient had three. *Streptococcus pneumoniae* was the most common pathogen. It was isolated in 14 of the 25 (56%) piperacillin/tazobactam patients, and 13 of the 27 (48%) co-amoxiclav/aminoglycoside patients. The second most common pathogen was *Haemophilus influenzae*, which

was detected in four patients in each group. Twenty other pathogens were identified: *Staphylococcus aureus* ( $n=7$ ), *Escherichia coli* ( $n=3$ ), *Streptococcus pyogenes* ( $n=3$ ), *Haemophilus* spp. ( $n=2$ ), *Klebsiella oxytoca* ( $n=2$ ), *Klebsiella pneumoniae* ( $n=1$ ), *Moraxella catarrhalis* ( $n=1$ ), and *Streptococcus milleri* ( $n=1$ ).

Fourteen patients (32%) in the piperacillin/tazobactam group had positive blood cultures compared to 12 (27%) in the co-amoxiclav/aminoglycoside group. Three patients in the piperacillin/tazobactam group and one in the co-amoxiclav/aminoglycoside group harboured *Staphylococcus epidermidis*, which was considered a contaminant. In all four cases there was heavy growth of respiratory pathogens in the sputum cultures: *Streptococcus pneumoniae* ( $n=2$ ), *Moraxella catarrhalis* ( $n=1$ ), and *Haemophilus influenzae* ( $n=1$ ). The 11 piperacillin/tazobactam patients with possibly true-positive blood cultures harbored the following microorganisms: *Streptococcus pneumoniae* ( $n=8$ ), *Haemophilus influenzae* ( $n=1$ ), *Escherichia coli* ( $n=1$ ), and *Staphylococcus aureus* ( $n=1$ ). The possibly true-positive blood cultures of the 11 aforementioned co-amoxiclav/aminoglycoside patients grew the following microorganisms: *Streptococcus pneumoniae* ( $n=9$ ), *Streptococcus pyogenes* ( $n=1$ ), and *Klebsiella pneumoniae* ( $n=1$ ). Only one strain of *Staphylococcus aureus* in the piperacillin/tazobactam group was resistant to amoxicillin.

**Table 3** Bacteriological efficacy in evaluable patients treated with either piperacillin/tazobactam or co-amoxiclav/aminoglycoside

	No. (%) of patients		
	PIP/TAZ group (n = 25)	Co-AMX/amino group (n = 27)	P value
Eradication (documented)	14 (56)	14 (52)	0.49
Eradication (presumed)	10 (40)	11 (40)	>0.5
Indeterminate	1 (4)	0	0.48
Persistence (documented)	0	1 (4)	>0.5
Persistence (presumed)	0	1 (4)	>0.5

PIP, piperacillin; TAZ, tazobactam; Co-AMX, co-amoxiclav; amino, aminoglycoside.

Not unexpectedly, seven strains of *Streptococcus pneumoniae* (1 in the piperacillin/tazobactam group and 6 in the co-amoxiclav/aminoglycoside group) were resistant to aminoglycosides.

The bacteriological efficacy at cessation of antibacterial therapy in the 52 evaluable patients is shown in Table 3. A favorable bacteriological response (documented or presumed eradication of the baseline pathogen) was observed in 24 of 25 (96%) evaluable patients in the piperacillin/tazobactam group and in 25 of 27 (92%) patients in the co-amoxiclav/aminoglycoside group ( $P=0.53$ ). Persistence of the baseline pathogen at study cessation occurred in two patients in the co-amoxiclav/aminoglycoside group (both *Klebsiella oxytoca*, 1 case documented and 1 presumed).

**Adverse Events.** Four adverse events were registered: one in the piperacillin/tazobactam group and three in the co-amoxiclav/aminoglycoside group (2% vs. 7%;  $P=0.32$ ). The only adverse event occurring in the piperacillin/tazobactam group – an elevated SGPT/SGOT serum level – was considered to be possibly due to the antibacterial regimen. In the co-amoxiclav/aminoglycoside group, acute renal failure ( $n=2$ ) and fever of  $38.5^{\circ}\text{C}$  ( $n=1$ ) were considered to be remotely or possibly drug related.

## Discussion

The results of the present trial indicate that piperacillin/tazobactam is highly efficacious in the treatment of serious pneumonia in hospitalized patients. Its clinical efficacy was at least as good as co-amoxiclav plus aminoglycoside. Whereas the clinical cure rate was slightly (but not significantly) higher in the piperacillin/tazobactam group (81%) compared to the co-amoxiclav/aminoglycoside group (65%), the overall favorable response rate was equal with both regimens. Furthermore, the piperacillin/tazobactam regimen was as good as the comparator therapy with respect to the eradication of baseline pathogens.

Interestingly, although the severity of the pneumonia was comparable in both patient groups (Table 1), the mortality was lower in the piperacillin/tazobactam

(2.4%) than in the co-amoxiclav/aminoglycoside group (14%). The difference almost reached statistical significance ( $P=0.059$ ). Thus, the mortality rate in the piperacillin/tazobactam group was quite low considering the fact that our study included only patients with serious pneumonia as defined in the Methods section. The possibly drug-related adverse events were non-significantly lower with the piperacillin/tazobactam treatment (2%) than with the co-amoxiclav/aminoglycoside regimen (7%;  $P=0.32$ ).

The increasing prevalence of  $\beta$ -lactamase-producing microbes has reduced the clinical efficacy of piperacillin as a monosubstance [4]. The association of the  $\beta$ -lactamase inhibitor tazobactam with piperacillin restores the activity of the latter to a very considerable degree, as demonstrated by a number of trials [5–7] and by recent worldwide surveys indicating good in vitro activity of this combination against gram-negative and gram-positive aerobic and anaerobic organisms (A.P. Pallett and M.P. Carroll, 6th International Congress for Infectious Diseases, Prague, 1994, Abstract no. 857; M. Joshi et al. 6th ICID, Prague, 1994, Abstract no. 856) [10–13]. The spectrum of activity of piperacillin/tazobactam extends to most pathogens encountered in severe bacterial pneumonia. This combination has recently been investigated in two non-comparative trials in patients with mild to moderate pneumonia [8, 9]. In both of these studies, the combination therapy was found to be clinically and bacteriologically efficacious, well-tolerated and safe. The present trial provides evidence that this applies also to patients with serious pneumonia. Our results are in accordance with two other randomized, comparative trials that have shown that, in this same indication, piperacillin/tazobactam is as effective as cefuroxime (A.P. Pallett and M.P. Carroll, 6th ICID, Prague, 1994, Abstract no. 857), and more effective than ceftazidime (M. Joshi et al., 6th ICID, Prague, 1994, Abstract no. 856), regarding both clinical and microbial efficacy.

In these trials the safety assessments of the piperacillin/tazobactam association were also favorable, and the results were independent of the co-administration of aminoglycosides. These latter drugs are often administered in combination with other antibacterial substances for treatment of severe nosocomial infections. Their use is

associated with toxicity and increased costs for monitoring drug serum levels and renal function. Therefore, the development of equally effective combinations not containing aminoglycosides would be advantageous. The present study was designed to provide a direct comparison between piperacillin/tazobactam and a standard drug combination, namely co-amoxiclav plus an aminoglycoside. Our results indicate that the piperacillin/tazobactam combination compares favorably with co-amoxiclav plus an aminoglycoside. Moreover, costly monitoring of renal function and drug serum levels are not required with the piperacillin/tazobactam treatment.

In conclusion, the present clinical trial indicates that piperacillin/tazobactam is highly efficacious and safe for the treatment of serious pneumonia in hospitalized patients. It further demonstrates that this drug combination compares favorably with that of co-amoxiclav plus an aminoglycoside.

**Acknowledgements** The authors are indebted to Prof. F.H. Kayser for his critical review of the paper, and to Lederle, a Division of American Home Products (Switzerland) Ltd. for their financial support of the study.

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